

10/670,744

L12 ANSWER 1 OF 10 CAPLUS COPYRIGHT 2005 ACS on STN

AN 2003:591035 CAPLUS

DN 139:143973

TI 6-Fluorobicyclo[3.1.0]hexane derivatives

IN Nakazato, Atsuro; Chaki, Shigeyuki; Sakagami, Kazunari; Dean, Ryoko; Ohta, Hiroshi; Hirota, Shiho; Yasuhara, Akito

PA Taisho Pharmaceutical Co.,ltd., Japan

SO PCT Int. Appl., 98 pp.

CODEN: PIXXD2

DT Patent

LA Japanese

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2003061698	A1	20030731	WO 2002-JP13693	20021226 <--
	W:				
	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW:				
	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	CA 2471642	AA	20030731	CA 2002-2471642	20021226 <--
	EP 1459765	A1	20040922	EP 2002-793421	20021226
	R:				
	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
	BR 2002015462	A	20041130	BR 2002-15462	20021226
	US 2005119345	A1	20050602	US 2003-500101	20021226
PRAI	JP 2001-395797	A	20011227		
	WO 2002-JP13693	W	20021226		

OS MARPAT 139:143973

IT 569686-58-4P

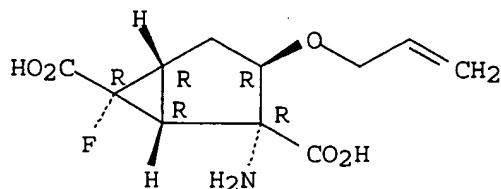
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(6-Fluorobicyclo[3.1.0]hexane derivs. having group II metabotropic glutamate receptor antagonist actions as antidepressants)

RN 569686-58-4 CAPLUS

CN Bicyclo[3.1.0]hexane-2,6-dicarboxylic acid, 2-amino-6-fluoro-3-(2-propenyloxy)-, (1R,2R,3R,5R,6R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RE.CNT 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

DERWENT-ACC-NO: 2003-663366

DERWENT-WEEK: 200537

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TITLE: 6-Fluorobicyclo(3.1.0)hexane derivatives are  
group II  
metabotropic glutamate receptor antagonist  
useful as  
antidepressants

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K[SAKAI],  
YASUHARA A[YASUI]

PRIORITY-DATA: 2001JP-0395797 (December 27, 2001)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE
PAGES MAIN-IPC		
US 20050119345 A1	June 2, 2005	N/A
000 A61K 031/195		
WO 2003061698 A1	July 31, 2003	J
096 A61K 045/00		
AU 2002359923 A1	September 2, 2003	N/A
000 A61K 045/00		
EP 1459765 A1	September 22, 2004	E
000 A61K 045/00		
KR 2004068348 A	July 30, 2004	N/A
000 A61K 031/196		
BR 200215462 A	November 30, 2004	N/A
000 A61K 045/00		
JP 2003561641 X	May 19, 2005	N/A
073 C07C 229/50		

DESIGNATED-STATES: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO  
CR CU CZ  
DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP  
KR KZ LC  
LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SC  
SD SE SG

SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW AT BE BG CH CY  
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 EA EE ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SI  
 SK SL SZ  
 TR TZ UG ZM ZW AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR IE IT LI  
 LT LU LV  
 MC MK NL PT RO SE SI SK TR

APPLICATION-DATA:

PUB-NO	APPL-DESCRIPTOR	APPL-NO
APPL-DATE		
US20050119345A1	N/A	2002WO-JP13693
December 26, 2002		
US20050119345A1	N/A	2005US-0500101
February 4, 2005		
WO2003061698A1	N/A	2002WO-JP13693
December 26, 2002		
AU2002359923A1	N/A	2002AU-0359923
December 26, 2002		
AU2002359923A1	Based on	WO2003061698
N/A		
EP 1459765A1	N/A	2002EP-0793421
December 26, 2002		
EP 1459765A1	N/A	2002WO-JP13693
December 26, 2002		
EP 1459765A1	Based on	WO2003061698
N/A		
KR2004068348A	N/A	2004KR-0710069
June 25, 2004		
BR 200215462A	N/A	2002BR-0015462
December 26, 2002		
BR 200215462A	N/A	2002WO-JP13693
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BR 200215462A	Based on	WO2003061698
N/A		
JP2003561641X	N/A	2002WO-JP13693
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JP2003561641X	N/A	2003JP-0561641
December 26, 2002		
JP2003561641X	Based on	WO2003061698
N/A		

INT-CL (IPC): A61K031/194, A61K031/195 , A61K031/196 ,  
 A61K031/1966 ,  
 A61K031/225 , A61K031/381 , A61K031/3811 , A61K045/00 ,  
 A61P009/10 ,  
 A61P025/00 , A61P025/08 , A61P025/14 , A61P025/16 , A61P025/18 ,  
 A61P025/188 , A61P025/22 , A61P025/24 , A61P025/28 , A61P025/30 ,  
 A61P043/00 , A61P043/000 , C07C229/32 , C07C229/50 , C07C229/500

C07C237/04 , C07C237/24 , C07C255/54 , C07C255/544 , C07D333/16 ,  
C07D333/166

ABSTRACTED-PUB-NO: WO2003061698A

BASIC-ABSTRACT:

NOVELTY - 6-Fluorobicyclo(3.1.0)hexane derivatives (I) and their salts and hydrates are new.

DETAILED DESCRIPTION - 6-Fluorobicyclo(3.1.0)hexane derivatives of formula (I) and their salts and hydrates are new.

R1, R2 = H, 1-10C alkoxy, phenoxy, OAlk (optionally substituted by OAlk or 1 or 2 phenyl), 2-6C hydroxyalkoxy, NQQ or NR6CHR7AC00R8;

Alk = 1-6C alkyl;

Q = H, Alk, AlkOAlk, 2-6C hydroxyalkyl or AlkCOAlk);

R6, R7 = H, Alk (substituted by OH, COOH, phenyl, hydroxyphenyl, naphthyl, heteroaryl, OAlk, SAlk or CONH2), 2-6C alkyl (substituted by NH2, guanidino or SH), 1-10C alkyl, phenyl, hydroxyphenyl or naphthyl; or

R6+R7 = CH2, CH2CH2 or (CH2)3;

R8 = H or carboxyl protecting group;

A = bond, CH2, CH2CH2 or (CH2)3;

R3 = 1-10C acyl, 1-6C acyl (substituted by OAlk, COOAlk, or COOH) 2-10C hydroxyacyl or COCHR7ANHR9;

R9 = H or amino protecting group;

R4, R5 = H, 1-10C alkyl, 2-10C alkenyl, naphthyl 5 membered heteroaryl containing at least one N or phenyl (optionally substituted by 1-5 halo, 1-10C alkyl, 1-10C alkoxy, CF3, phenyl, COOH, NH2, NO2, CN or phenoxy); or

R4+R5 = ring.

An INDEPENDENT CLAIM is also included for antidepressants comprising a group II metabotropic glutamate receptor antagonist.

ACTIVITY - Antidepressant; Tranquilizer, Nootropic; Vasotropic; Neuroprotective; Anticonvulsant; Antiparkinsonian; Cerebroprotective.

MECHANISM OF ACTION - Glutamate-Antagonist.

In assays using CHO cells (1R,2R,3R,5R,6R)-2-amino-3-methoxy-6-fluorobicyclo(3.1.0)hexane-2,6-dicarboxylic acid had an IC50 value for (3H)-MGS00008 binding at glutamate MGLuR2 receptors of less than 100 nM (no specific value is given).

USE - (I) is used as group II metabotropic glutamate receptor antagonists for treating and preventing depression. (I) may also be useful for treating and preventing e.g. anxiety, bipolar diseases, Alzheimer's disease, Huntington's chorea, Parkinson's diseases, amyotrophic lateral sclerosis, ischemia, cerebral insufficiency, head trauma or spinal cord disorders.

CHOSEN-DRAWING: Dwg.0/2

TITLE-TERMS: HEXANE DERIVATIVE GROUP GLUTAMATE RECEPTOR ANTAGONIST  
USEFUL

ANTIDEPRESSANT

DERWENT-CLASS: B05

CPI-CODES: B06-H; B07-H; B10-A15; B10-A17; B10-B01; B10-B02; B10-B03; B10-B04;  
B10-C02; B10-C03; B10-C04; B10-D01; B10-D03; B14-F02D;  
B14-J01A1;  
B14-J01A3; B14-J01A4; B14-J01B3; B14-J01B4; B14-L06; B14-N16;  
B14-N17B; B14-S01;

CHEMICAL-CODES:

Chemical Indexing M2 \*01\*

Fragmentation Code

G031 G033 G038 G039 G060 G600 H1 H100 H161 H5  
H561 H6 H601 H661 H8 J0 J012 J1 J152 M210  
M211 M272 M281 M320 M415 M510 M520 M530 M541 M710  
M904 M905 P444 P446 P448 P451 P517 P528 P617 P625

P942  
Ring Index  
00695  
Specific Compounds  
ABLD8T ABLD8N

Chemical Indexing M2 \*02\*

Fragmentation Code

D010 D019 D020 D029 D040 D049 F010 F011 F012 F019  
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G012 G013 G019 G020 G021 G029 G031 G033 G038 G039  
G050 G111 G112 G113 G221 G299 G600 H100 H101 H141  
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H484 H498 H5 H521 H541 H542 H561 H581 H582 H583  
H584 H598 H599 H6 H601 H608 H609 H641 H642 H661  
H685 H689 H721 H722 H8 J0 J011 J012 J013 J014  
J111 J112 J131 J132 J171 J172 J173 J211 J212 J241  
J242 J251 J252 J271 J3 J341 J342 J351 J352 J361  
J371 J372 J373 J451 J452 J471 J581 J582 J583 L143  
L199 L250 L299 L640 L660 L699 M111 M119 M121 M122  
M123 M124 M125 M126 M129 M132 M135 M136 M139 M141  
M149 M150 M210 M211 M212 M213 M214 M215 M216 M220  
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M262 M271 M272 M273 M280 M281 M282 M283 M311 M312  
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M333 M334 M340 M342 M343 M344 M349 M353 M371 M372  
M373 M381 M383 M391 M392 M393 M412 M413 M414 M415  
M510 M511 M512 M513 M520 M521 M522 M523 M530 M531  
M532 M533 M541 M630 M640 M650 M710 M904 M905 P444  
P446 P448 P451 P517 P528 P617 P625 P942

Ring Index

00695

Markush Compounds

200107-28201-T 200107-28201-N

SECONDARY-ACC-NO:

CPI Secondary Accession Numbers:

C2003-180168



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(19) **United States**(12) **Patent Application Publication**

Nakazato et al.

(10) **Pub. No.: US 2005/0119345 A1**(43) **Pub. Date: Jun. 2, 2005**(54) **6-FLUOROBICYCLO[3.1.0]HEXANE  
DERIVATIVES**

(57)

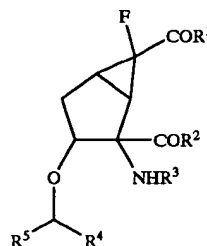
**ABSTRACT**

(76) Inventors: Atsuro Nakazato, Tokyo (JP);  
Shigeyuki Chaki, Tokyo (JP);  
Kazunari Sakagami, Tokyo (JP);  
Ryoko Dean, Tokyo (JP); Hiroshi  
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An antidepressant comprising, as an active ingredient, a compound having an antagonistic effect on group II metabotropic glutamate receptors, as well as a 2-amino-3-alkoxy-6-fluoro-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid derivative of Formula [I]:

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[I]



(21) Appl. No.: 10/500,101

(22) PCT Filed: Dec. 26, 2002

(86) PCT No.: PCT/JP02/13693

(30) **Foreign Application Priority Data**

Dec. 27, 2001 (JP) ..... 2001-395797

**Publication Classification**

(51) Int. Cl.⁷ ..... A61K 31/195; C07C 229/32

(52) U.S. Cl. .... 514/561; 562/502

[wherein R¹ and R², which may be the same or different, each represent a hydroxyl group, a C<sub>1-10</sub> alkoxy group, etc.; R³ represents a C<sub>1-10</sub> acyl group, a C<sub>1-6</sub> alkoxy-C<sub>1-6</sub> acyl group, etc.; and R⁴ and R⁵, which may be the same or different, each represent a hydrogen atom, a C<sub>1-10</sub> alkyl group, etc.] or a pharmaceutically acceptable salt or hydrate thereof.

give (1R,2R,3R,5R,6R)-2-amino-3-((R\*)-1-(naphthalen-2-yl)ethoxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid 2-benzyl ester 6-ethyl ester (164 mg) and (1R,2R,3R,5R,6R)-2-amino-3-((S\*)-1-(naphthalen-2-yl)ethoxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid 2-benzyl ester 6-ethyl ester (153 mg), respectively.

[0120] (3) Starting with (1R,2R,3R,5R,6R)-2-amino-3-((R\*)-1-(naphthalen-2-yl)ethoxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid 2-benzyl ester 6-ethyl ester (158 mg) and (1R,2R,3R,5R,6R)-2-amino-3-((S\*)-1-(naphthalen-2-yl)ethoxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid 2-benzyl ester 6-ethyl ester (148 mg), the same procedure as shown in Example 2(3) was repeated to give (1R,2R,3R,5R,6R)-2-amino-3-((R\*)-1-(naphthalen-2-yl)ethoxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (96.0 mg) and (1R,2R,3R,5R,6R)-2-amino-3-((S\*)-1-(naphthalen-2-yl)ethoxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (72.0 mg).

#### EXAMPLE 4

Synthesis of (1R,2R,3R,5R,6R)-2-amino-3-propyloxy-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid

[0121] (1) (1R,2R,3R,5R,6R)-2-Amino-3-(2-propenyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (40 mg) was dissolved in water (1 mL). To this solution, 10% palladium/carbon (4 mg) was added and stirred under a hydrogen atmosphere at room temperature for 2 days. After the catalyst was filtered off, the filtrate was concentrated under reduced pressure, followed by addition of tetrahydrofuran (1 mL) and heating at reflux for 1 hour. The reaction mixture was stirred at room temperature for an additional 3 hours, filtered to remove any solids, and then purified on an ion-exchange resin (AG 50W-X8 Resin (H-type), developing solvent: water, 50% aqueous tetrahydrofuran, 10% aqueous pyridine) to give (1R,2R,3R,5R,6R)-2-amino-3-propyloxy-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (30 mg).

#### EXAMPLE 5

Synthesis of (1R,2R,3R,5R,6R)-2-amino-3-cyclopentyloxy-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid

[0122] (1) Starting with crude 2-cyclopentenyl-2,2,2-trichloro-acetimidate (375 mg) prepared from 2-cyclopenten-1-ol and (1R,2R,3R,5R,6R)-2-azide-3-hydroxy-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid 2-benzyl ester 6-ethyl ester (650 mg), the same procedure as shown in Example 2(1) was repeated to give (1R,2R,3R,5R,6R)-2-azide-3-(2-cyclopentyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid 2-benzyl ester 6-ethyl ester (339 mg).

[0123] <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ (ppm); 1.32 (3 H, t, J=7.3 Hz), 1.90-2.52 (8 H, m), 3.94-4.14 (1 H, m), 4.27 (2 H, q, J=7.3 Hz), 4.52-4.79 (1 H, m), 5.15-5.41 (2 H, m), 5.58-5.82 (1 H, m), 5.88-6.04 (1 H, m), 7.30-7.46 (5 H, m).

[0124] MS(ESI)(Pos)m/z; 452 (M+Na)<sup>+</sup>

[0125] (2) (1R,2R,3R,5R,6R)-2-Azide-3-(2-cyclopentyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid 2-benzyl ester 6-ethyl ester (331 mg) was dissolved in acetic

acid (18 mL) and water (6 mL). To this solution, 10% palladium/carbon (39 mg) was added and stirred under a hydrogen atmosphere at room temperature for 24 hours. After the catalyst was filtered off, the filtrate was concentrated under reduced pressure. The resulting residue was dissolved in tetrahydrofuran (7.36 mL) and water (3.53 mL), followed by addition of lithium hydroxide hydrate (80 mg) and stirring at room temperature for 4 hours. After the solvent was distilled off under reduced pressure, the resulting residue was purified on an ion-exchange resin (AG 50W-X8 Resin (H-type), developing solvent: water, 50% aqueous tetrahydrofuran, 10% aqueous pyridine) to give (1R,2R,3R,5R,6R)-2-amino-3-cyclopentyloxy-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (61 mg).

#### EXAMPLE 6

Synthesis of (1R,2R,3R,5R,6R)-2-amino-3-(3-nitrobenzyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester, (1R,2R,3R,5R,6R)-2-amino-3-(3-aminobenzyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester and (1R,2R,3R,5R,6R)-2-amino-3-(3-aminobenzyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid

[0126] (1) Starting with crude 3-nitrobenzyl-2,2,2-trichloro-acetimidate (562 mg) prepared from 3-nitrobenzyl alcohol and (1R,2R,3R,5R,6R)-2-azide-3-hydroxy-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester (380 mg), the same procedure as shown in Example 2(1) was repeated to give (1R,2R,3R,5R,6R)-2-azide-3-(3-nitrobenzyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester (279 mg).

[0127] <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ (ppm); 1.32 (3 H, t, J=7.2 Hz), 1.34 (3 H, t, J=7.2 Hz), 2.22-2.42 (2 H, m), 2.50 (2 H, dd, J=2.7, 7.8 Hz), 3.94-4.10 (1 H, m), 4.20-4.46 (4 H, m), 4.58 (1 H, d, J=12.1 Hz), 4.80 (1 H, d, J=12.1 Hz), 7.44-7.66 (2 H, m), 8.03-8.24 (2 H, m).

[0128] MS(ESI)(Pos)m/z; 459 (M+Na)<sup>+</sup>

[0129] (2) Starting with (1R,2R,3R,5R,6R)-2-azide-3-(3-nitrobenzyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester (275 mg), the same procedure as shown in Example 2(2) was repeated to give (1R,2R,3R,5R,6R)-2-amino-3-(3-nitrobenzyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester (120 mg).

[0130] (3) (1R,2R,3R,5R,6R)-2-Amino-3-(3-nitrobenzyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester (120 mg) was dissolved in acetic acid (0.21 mL). To this solution, zinc powder (101 mg) was added and stirred at room temperature for 3 hours. The reaction mixture was filtered to remove any solids, followed by addition of ice-cold saturated sodium bicarbonate. After the reaction mixture was extracted twice with ethyl acetate, the combined organic layers were washed with 0.5 M aqueous sodium carbonate and saturated aqueous sodium chloride, and then dried over anhydrous sodium sulfate. After the drying agent was filtered off, the filtrate was concentrated under reduced pressure and the resulting residue was purified by column chromatography (silica gel: Wako gel C200, developing solvent: chloroform/ethanol=30/1) to give (1R,2R,3R,5R,6R)-2-amino-3-(3-aminobenzyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester (96 mg).